Prenatal Ultrasound to Detect Fetal Anomalies
Douglas S. Richards
Neoreviews 2012;13;e9
DOI: 10.1542/neo.13-1-e9

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://neoreviews.aappublications.org/content/13/1/e9
Prenatal Ultrasound to Detect Fetal Anomalies

Douglas S. Richards, MD*

Abstract
Fetal ultrasound imaging has become an indispensable tool in obstetric practice. In spite of early reports revealing a low sensitivity for diagnosing birth defects, ultrasound has become established as a safe and widely used screening test, best performed at about 20 weeks’ gestation. To maximize effectiveness of ultrasound screening, proper sonographer training and quality assurance is essential. Patients undergoing prenatal ultrasound should be made aware of the limitations of this tool for detecting anomalies. Prenatal detection has several practical benefits, including parental preparation, delivery planning, and optimal pediatric care. Effective noninvasive screening tests for aneuploidies have been developed and are superior to maternal age alone as a method of identifying candidates for invasive testing.

Objectives After completing this article, the reader should be able to:
1. Understand how the prenatal diagnosis of fetal birth defects affects obstetric and neonatal care.
2. Gain perspective on the accuracy of prenatal ultrasound for diagnosing birth defects.
3. Understand how ultrasound screening for birth defects is incorporated into obstetrical practice.
4. Gain insight into the types of defects that are detectable by seeing ultrasound images of anomalous fetuses.

Introduction
Almost no other tool has affected the practice of obstetrics as much as diagnostic ultrasound. This window to the fetus has expanded the focus of obstetrics to include the fetus as a second patient. Ultrasound first was used in obstetrics by Scotsman Ian Donald in the late 1950s but did not come into widespread clinical use until the late 1970s. The earliest practical use in obstetrics was to estimate the fetal age by measuring the biparietal diameter. Other important information that could be gained with early low-resolution machines included confirmation of viability, diagnosis of multiple gestations, determination of the fetal lie, assessment of amniotic fluid volume, and recognition of placental abnormalities. One of the most important uses of obstetric ultrasound that has emerged is to diagnose fetal malformations, the focus of this article.

Initially, two-dimensional ultrasound was only capable of producing static, low-resolution images, with no gradations of grey. These images were made by collating reflected sound waves produced and received by a transducer that was passed over the mother’s abdomen in one plane. The location of the structures giving off echoes was determined by the send-receive interval of the sound pulses and the relative position of the transducer. With laborious adjustments of the scanning plane, basic aspects of the intrauterine contents could be evaluated. Tables were developed that allowed the gestational age to be inferred from the size of the head and abdomen. Subsequently, regression equations involving these measurements were used to estimate fetal weight. In that era, it was possible to diagnose some malformations that involved major disruption of fetal anatomy. Birth defects that could be diagnosed included such conditions as hydrocephalus, anencephaly, and omphalocele.

*Clinical Professor of Obstetrics, University of Utah College of Medicine; Division of Maternal Fetal Medicine, University of Utah and Intermountain Medical Center, Salt Lake City, UT.
The availability of real-time ultrasound imaging in the early 1980s greatly expanded the ability of sonographers to visualize and diagnose structural defects in the fetus. In that era there were a large number of case reports and small series entitled “Prenatal ultrasound diagnosis of …”. The importance of real-time ultrasound for diagnosing fetal anomalies cannot be overemphasized. With other body imaging modalities, the patient is put in a standard position, and predefined sets of images are obtained. The technician must know how to obtain these standard images, but in most cases there is no real-time adjustment of image planes. Images are interpreted later, off-line, by a radiologist. Obviously, the fetus is not in a “standard” position. There is no end to the possible positions a fetus (or fetuses!) can assume: cephalic, breech, or transverse, with back up, down, right side, left side, etc. Real-time ultrasound allows the experienced sonographer to make gross and fine adjustments of the transducer position and angle to obtain desired fetal images. Over the past few decades, other technological advances have greatly improved the ability of the sonographer to resolve fine detail of fetal anatomic structures.

With these advances, expansion of ultrasound usage to routinely screen for fetal anomalies was inevitable. In the early days of ultrasound (ie, before the mid-1980s), prenatal ultrasound examinations were ordered only for specific indications. These included such conditions as uncertain gestational age, suspected macrosomia or growth restriction, and vaginal bleeding. As it became possible to diagnose fetal malformations with ultrasound, being at risk for a birth defect became an indication for performing a scan. Accepted risk factors included such things as a positive family history of a structural defect, maternal exposure to a teratogenic drug, advanced maternal age, and an elevated maternal serum α-fetoprotein level.

By the 1990s, given the apparent safety, availability, and expanding capabilities of diagnostic ultrasound, there was growing interest in more widespread use of ultrasound in pregnancy. The concept arose that screening ultrasound examinations should be offered to all pregnant women. The desirability of such a development may seem obvious to pregnant women and their caregivers. Every expectant woman wonders “Will my baby be OK?”, and this noninvasive test seemed to be an ideal way to answer this question. However, the same concerns pertain to ultrasound as to any other screening test. Is it safe and widely available at a reasonable cost? Does it have high sensitivity and acceptable specificity? Are there follow-up diagnostic tests that can distinguish true- from false-positives? Perhaps most importantly, are there effective interventions that can be used when an abnormality is identified? These questions must be satisfactorily answered if ultrasound is to be considered an appropriate screening test for birth defects.

Safety Concerns
First, is it safe for the fetus to be exposed to the acoustic energy associated with diagnostic ultrasound? As sound waves are absorbed by maternal and fetal tissue, they are converted into heat. In physical therapy, this phenomenon is used therapeutically. Laboratory experiments have revealed that the type of ultrasound used for diagnostic testing can damage tissue through the formation of micro bubbles and a phenomenon called cavitation. Fortunately, these do not occur with the relative low energy intensity used with diagnostic ultrasound. As early as the mid-1970s, researchers had concluded that there was no significant biologic effect from ultrasound as used in diagnostic settings. In spite of this, ongoing research has sought to identify any previously unrecognized risks. So far, no significant harm has been uncovered, leading the American Institute of Ultrasound in Medicine (AIUM) to issue formal statements on the safety of diagnostic ultrasound. The most recent pronouncement states “No independently confirmed adverse effects caused by exposure from present diagnostic ultrasound instruments have been reported in human patients…” (Official Statement, Prudent Use and Clinical Safety, AIUM, March 2007). However, the AIUM position has always been that because of the remote possibility of unrecognized harm, ultrasound should only be used by qualified health professionals to provide medical benefit to the patient. This leads to the conclusion that fetal ultrasound should not be used for “entertainment” purposes. The AIUM and American College of Obstetricians and Gynecologists issued a joint statement stating that “The use of ultrasound without a medical indication to view the fetus, obtain a picture of the fetus or determine the fetal gender is inappropriate and contrary to responsible medical practice.”

Reliability of Diagnosing Defects
What about the sensitivity and specificity of ultrasound to diagnose birth defects? Many patients and families incorrectly assume that when they have had a “normal” ultrasound examination, serious fetal anomalies have been ruled out. There seemed to be support for this optimistic view from several studies from the late 1980s and early 1990s that revealed anomaly detection rates of >75%. However, these high detection rates were reported from centers that were at the cutting edge of ultrasound diagnostics. A sobering National Institutes of Health-sponsored
multicenter randomized trial of routine ultrasound involving 15,000 women (the “RADIUS” study, published in 1993) revealed a disappointing low sensitivity for the detection of birth defects in low-risk women, especially in a community setting. In the RADIUS trial, only 17% of major anomalies were diagnosed before 24 weeks, and only 35% were diagnosed when a third trimester repeat examination was included in the testing scheme. Partly based on this low sensitivity, the authors of that study concluded that routine ultrasound screening of pregnant women was not efficacious. Detection rates were somewhat better in a large multicenter European study of 200,000 women (the “Eurofetus” study, published in 1999) in which the authors detected 61% of malformations.

Because many factors must be taken into account, it is fairly difficult to pin down figures for the sensitivity of ultrasound for diagnosing birth defects. What is the skill and experience of the examiners? What should be considered “significant” malformations (Do extra digits and ear tags count?). What about genetic diseases that do not have gross structural manifestations? When in gestation is the ultrasound done? Is it repeated? How thorough is the ascertainment of birth defects in neonates, especially considering that serious defects such as congenital heart disease may not be diagnosed until after hospital discharge?

In spite of these questions and limitations, several conclusions can be drawn. First, some malformations are much easier to diagnose than others. For example, in the Eurofetus study, 88% of major anomalies involving the central nervous system and urinary tract were diagnosed, compared with only 18% of cleft lip and palate. Secondly, as expected, the sensitivity of ultrasound as a screen depends on the experience of examiners. In the RADIUS study, the detection rate was three times higher in an academic center than in general obstetrical or radiology practices. Although not yet proven by large-scale studies, it seems that detection of birth defects has improved considerably over the years. Affordable, high-resolution equipment is widely available, and there has been much progress in sonographer training and quality assurance for ultrasound clinics. In the 1980s, many clinicians bought machines and, with surprisingly limited training, started using ultrasound for the “basic” functions of obtaining measurements, determining fetal lie, and so on. In many of these clinics, no systematic evaluation of fetal anatomy was performed and no formal reports were generated. Nevertheless, patients often were left with the erroneous impression that an adequate screen for birth defects had been performed. Recognizing that this is an unsatisfactory situation, the AIUM has issued formal guidelines regarding standards for obstetric ultrasound examinations. These standards cover such issues as credentialing of providers, quality of equipment, and adequacy of reports and image storage. The AIUM position is that physicians who perform or interpret obstetrical ultrasounds should complete an approved training program, have continuing education in the field, and be involved with an adequate number of cases each year to ensure continued competency. Voluntary AIUM certification of an ultrasound practice also requires that ultrasound technicians complete approved training programs and obtain registered diagnostic medical sonographer certification.

In terms of diagnosing birth defects, ultrasound has been shown to have a high specificity, that is, when the fetus is normal the ultrasound is almost always interpreted as being normal. This is fortunate, since false-positive diagnoses cause considerable parental distress and lead to unnecessary follow-up tests. When a screening ultrasound is suspicious for an anomaly, the patient is referred to a specialist, usually a maternal fetal medicine physician or radiologist with special expertise in diagnosing fetal malformations. With this “diagnostic” ultrasound, the specific nature of the anomaly (if any) can be worked out and the patient can be counseled appropriately. Many referrals to a specialist center are not based on findings that show a definite abnormality but are a result of a screening examination that “doesn’t look quite right.” Although this situation causes temporary worry, concerns can usually be quickly laid to rest by the specialist. There are findings that even the specialist determines to be outside the range of normal but which have uncertain significance. Examples of this include mild dilation of the renal pelves or mild dilation of the cerebral ventricles. In such instances, it is necessary to do repeated examinations in which case the significance of the findings will eventually become evident. Another class of ultrasound findings that can cause a high degree of patient anxiety includes “markers” for fetal aneuploidy. These are relatively common in normal fetuses, but their presence indicates an increased risk of Down syndrome. They will be discussed later.

Number, Timing of Ultrasound Examinations

If ultrasound is to be used to screen for birth defects, when should scans be performed? Naturally, it would be advantageous to diagnose serious birth defects as early as possible. However, only the most severely disruptive anomalies (such as anencephaly and large abdominal wall defects) can be diagnosed in the first trimester. Some
Benefits of Prenatal Birth Defect Diagnosis

Why make an effort to screen for and diagnose birth defects antenatally? One of the most important reasons is to give reassurance when the ultrasound examination or genetic tests are normal. This is especially important when a family knows that they are at high risk of having a child with a serious genetic disorder. Prenatal diagnosis is available for many if not most severely debilitating neurodegenerative diseases. Without the reassurance that prenatal testing can offer, at-risk parents may not feel safe in attempting a pregnancy at all. In contrast to many definitive DNA-based tests for genetic diseases, ultrasound screening for structural birth defects is usually not definitive. However, studies have revealed that women have considerably reduced anxiety levels after a normal ultrasound examination.

Another advantage of prenatal diagnosis is that it allows for optimal delivery planning. Obviously, an anomalous infant should be born in a setting where he or she can receive the level of care that he or she needs, especially if emergency intervention is going to be required. The delivery can be planned at a time when appropriate personnel and resources are immediately available. For example, a fetus with hypoplastic left heart syndrome and a restrictive foramen ovale should deliver with an invasive cardiologist on standby to perform an immediate atrial septostomy. A fetus with severe diaphragmatic hernia should deliver at a center that has extracorporeal membrane oxygenation available. The optimal delivery mode may depend on the presence of certain defects. For example, a fetus with a sacrococcygeal teratoma or severe hydrocephalus cannot be safely delivered vaginally. Conversely, the potential morbidity from a cesarean delivery should be avoided when the fetus with a lethal anomaly has nothing to gain from an abdominal delivery. This would obviously be the case for a fetus with anencephaly. Another benefit of prenatal diagnosis of birth defects is that condition of some fetuses may deteriorate in utero. If clinicians are aware of the problem in advance, appropriate surveillance and intervention can be instituted. For example, although live-born infants with gastroschisis have a very good chance of intact survival, there is a significant risk of fetal death. With intensive antenatal monitoring, compromise of the fetal status can often be recognized, and the infant can be delivered expeditiously.

Prenatal diagnosis of certain defects can alert pediatricians of conditions that may be asymptomatic at birth. For example, a fetus found to have severe ureteropelvic junction obstruction or vesicoureteral reflux can be referred for urologic evaluation soon after birth, avoiding short- and long-term complications resulting from delayed diagnosis. Certain brain malformations can be detected prenatally that may be associated with either no or only subtle signs in the newborn period. If the defect is known before birth, early intervention with the infant may improve the ultimate neurologic outcome.

It is not uncommon for a woman to present to a specialist with a history of having had an infant who died of birth defects or a genetic disease that was never properly evaluated. All too often, distraught parents decline an autopsy, not realizing at the time the importance of a full genetic and anatomic evaluation. Without this vital information, it is difficult for clinicians to provide prospective parents accurate counseling regarding recurrence risks. When a problem is diagnosed prenatally, and a patient is referred to a prenatal diagnosis clinic, there is an increased chance that a correct diagnosis will be made and that arrangements can be made for any needed consultations and genetic tests.
Appropriate parental preparation for the delivery of a child with a birth defect is valuable. “Delivery room shock” is avoided when parents can be educated in advance about what to expect. They can then focus on the positive aspects of the birth instead of having to deal with the anxiety and stress from the unexpected problem. Even for conditions such as clubfoot or cleft lip, which are not life-threatening, it is helpful for parents to have the opportunity to meet with the professionals who will be caring for their newborn. With more serious conditions, patients can tour the ICU and become familiar with the care and procedures their infant will require. This preparation can reduce the confusion and anxiety that would come when dealing with a new diagnosis at a time when the infant is in a state of crisis. When a fetus has a genetic disease or birth defect for which there is little chance for survival beyond the early neonatal period, difficult decisions about the degree of care that will be provided are best made in advance. Some parents will choose to terminate a pregnancy when serious defects are known to be present. Others will continue the pregnancy, with a plan for palliative care of the infant. In these lethal cases, advance knowledge and preparation increase the chance that the parents can still have a positive experience with their newborn.

Examples of Birth Defects Diagnosed With Prenatal Ultrasound

An extensive review of birth defects that can be diagnosed with prenatal ultrasound is obviously beyond the scope of this article. However, to illustrate the types of conditions that can be diagnosed, examples from different categories of severity will now be discussed.

Very Limited Potential for Survival

One of the few birth defects that is unequivocally lethal is anencephaly (Fig 1). This is readily apparent at the time of the initial fetal survey. Other defects that are predictably lethal are those associated with no amniotic fluid in the last half of pregnancy. When there are no functioning kidneys, anhydramnios is inevitable. Responsible entities include bilateral renal agenesis, bilateral multicystic dysplastic kidneys (Fig 2), or, less commonly, autosomal recessive infantile polycystic kidney disease. The immediate cause of neonatal death in these conditions is pulmonary hypoplasia (Fig 3). Another cause of pulmonary hypoplasia and irreversible kidney damage is high-grade obstruction from posterior urethral valves in a male fetus. Other examples of conditions that are usually associated with very early death and limited mental development are certain chromosome abnormalities and brain malformations.
pointing to this diagnosis as well. The intracranial findings are often more apparent than the defect in the spine itself (Figs 6 and 7). Abnormal fluid collections in the brain are usually easy to spot, making the sensitivity of ultrasound high for detecting dilated ventricles or cystic brain lesions. Aqueductal stenosis manifests with dilation of the lateral and third ventricles (Fig 8). This can be severe and rapidly progressive, causing marked enlargement of the head and compression of the cerebral cortex. The neurologic prognosis is guarded with this and other structural abnormalities of the brain, such as the Dandy Walker malformation (Fig 9). The correlation between the apparent severity of the brain malformation and ultimate outcome for many conditions is variable, making counseling difficult.

Guarded Prognosis Requiring Immediate NICU Care

The largest group of conditions that falls into this category is congenital heart defects. With improved resolution of ultrasound equipment, improved skill of sonographers...
performing screening examinations, and the availability of specialists who can perform fetal echocardiography, it is now possible to accurately diagnose most fetal heart defects. The traditional method to screen for heart defects was to obtain the “four-chamber view” at a level that includes the atria, ventricles, and mitral and tricuspid valves. This view is good at showing aberrations in heart size and position, enlarged or underdeveloped ventricles (Fig 10), and large septal defects. To see conotruncal abnormalities, the transducer must be angled to see the outflow tracts (Fig 11). Visualization of the outflow tracts is now a suggested part of a routine screening ultrasound.

Diaphragmatic hernia is another condition for which prenatal diagnosis and immediate high-level neonatal care are important. It is mainly diagnosed by alteration in the position of the organs in the chest and abdomen (Fig 12). Abdominal wall defects, including gastroschisis and omphalocele, may be suspected from an elevated maternal serum alpha fetoprotein (MSAFP) and are usually easily seen with a 20-week screening ultrasound (Fig 13).
Conditions With Good Outcome, No Alteration in Pregnancy or Delivery

Two of the more common conditions that fall into this category are cleft lip (Fig 14) and clubfoot (Fig 15). A coronal view of the lower face is now considered standard, and this view readily shows cleft lip. An expert sonographer can usually determine whether this defect also involves the palate, but it is rare for an isolated cleft palate to be diagnosed with prenatal ultrasound. Clubfoot is easiest to see in the second trimester, when the fetal limbs are not constrained by the normal intrauterine crowding that occurs in late pregnancy. As previously noted, there are conditions such as ureteropelvic junction obstruction that may be silent at birth but for which prenatal diagnosis can prevent progressive damage. As with abnormal fluid collections in the brain, a dilated urinary system is easy to see (Fig 16).

Aneuploidy Screening With Ultrasound

Long before ultrasound was capable of showing detailed views of the fetus, diagnosis of fetal aneuploidy was possible with amniocentesis. This definitive diagnostic test is not constrained by the normal intrauterine crowding that occurs in late pregnancy. As previously noted, there are conditions such as ureteropelvic junction obstruction that may be silent at birth but for which prenatal diagnosis can prevent progressive damage. As with abnormal fluid collections in the brain, a dilated urinary system is easy to see (Fig 16).
has virtually 100% accuracy. Because of the expense and risk (\(\sim 1/300\) attributable pregnancy loss rate), amniocentesis is usually only performed in pregnancies at high risk for aneuploidy. More recently, chorionic villus sampling became available. Obviously, doing any testing for Down syndrome requires that the pregnant woman places a high value on knowing before birth that the fetus is affected. Traditionally, the high risk group that was offered invasive testing consisted of women age 35 or older. This age was selected because that was the age at which the chance of discovering aneuploidy was equivalent to the chance of causing pregnancy loss by doing the procedure (\(\sim 1/200\) at that time). Age itself is a poor screening test for aneuploidy because approximately two-thirds of affected infants are born to women <35 years old. In the 1980s and 1990s, various serum markers were discovered that were altered in the presence of some of the major aneuploidies. A screening test, commonly called the “quad test,” which used four of these chemical markers and maternal age, was developed. This test, performed at about 16 weeks’ gestation, detects 75% of trisomy 21 fetuses. Another pattern of the analytes detects many cases of trisomy 18. Women with a positive screen are offered amniocentesis. The specificity of the quad test is only 95%, meaning that 5% of women who carry normal fetuses will be screen positive. Because a risk of \(>1/270\) of Down syndrome is considered a positive test, most positive tests are false-positive.

Ultrasound has taken on an increasingly important role in screening for aneuploidy. Certain birth defects strongly point to trisomy 21. These include duodenal atresia (30% chance of Down syndrome; Fig 17) and atrioventricular septal defects (50% chance of trisomy 21; Fig 18). Although these birth defects are predictive of Down syndrome when present, the majority of infants with Down syndrome do not have these anomalies. Over the years, several ultrasound markers for Down syndrome have been identified. These are not birth defects per se but rather ultrasound signs that increase the likelihood that trisomy 21 is present. Likelihood ratios between 1.5 and 15 have been reported for these individual markers. These likelihood ratios can be used to calculate an ultrasound adjusted Down syndrome risk. The complete absence of any marker may reduce a woman’s a priori risk by \(>50\%\), and this may be...
sufficient reassurance for an otherwise high-risk woman to decide against amniocentesis. The most commonly used markers include thick nuchal skin (Fig 19), hypoplastic nasal bone, short femur or humerus, echogenic focus in the heart, echogenic bowel, and hydronephrosis. Unfortunately, 5% of normal fetuses have one or more of these markers. As expected, the presence of Down syndrome markers causes considerable parental anxiety.

Relatively recently, more sensitive and specific noninvasive screening tests have been developed. These consist of a first trimester serum test and an ultrasound performed at 11 to 13 weeks to measure the “nuchal translucency.” A combined first trimester screen that incorporates the ultrasound findings, chemical analytes, and maternal age has a sensitivity of 85%, with a specificity of 97%. When the second trimester serum components are added as well (a sequence of tests called the “integrated screen”), the sensitivity rises to over 90%. Recognizing the effectiveness of noninvasive screening tests, the American College of Obstetrics and Gynecology has recommended that they be offered to all pregnant women. Additionally, the American College of Obstetrics and Gynecology recommends abandonment of the old paradigm of using increased maternal age as an independent criterion for offering diagnostic testing (ie, amniocentesis or chorionic villus sampling). Instead, invasive diagnostic testing should be available to all pregnant women who will decide based on their personal assessment of the risks and benefits, which will almost always include the results of the noninvasive tests.

Conclusions
I hope that I have shown that ultrasound screening for birth defects is efficacious. It is sought after by almost all pregnant women. The majority of women in the United States now have a screening ultrasound at 18 to 20 weeks’ gestation. With appropriate training and up-to-date equipment, most serious birth defects can be diagnosed prenatally. However, a normal anatomy screen does not completely rule out the possibility of an anomaly. Screening for Down syndrome should be done after informed consent because many women are not motivated to diagnose this condition before birth, and false-positive screens are a problem. Noninvasive screening has made the use of invasive testing with amniocentesis much less common.

Figure 18. Atrioventricular septal defect in a fetus with trisomy 21. The left ventricle (LV) and common A-V valve are indicated (arrowheads).

Figure 19. Sagittal view of the neck showing thick skin in a fetus with trisomy 21.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications
• Know the rationale, methods, and interpretation of results of first and second trimester screening for aneuploidy (eg, nuchal translucency, clophexus cysts).
• Know the importance and limitations of ultrasonographic findings of common fetal anomalies including congenital heart disease.

SUGGESTED READING
Prenatal Ultrasound to Detect Fetal Anomalies
Douglas S. Richards

Neoreviews 2012;13:e9
DOI: 10.1542/neo.13-1-e9

Updated Information & Services
including high resolution figures, can be found at:
http://neoreviews.aappublications.org/content/13/1/e9

References
This article cites 20 articles, 6 of which you can access for free at:
http://neoreviews.aappublications.org/content/13/1/e9#BIBL

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Downloaded from http://neoreviews.aappublications.org/ by Robert Whipple on January 1, 2012